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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,676	12/01/1998	MICHAEL R. ZALUTSKY	00250.74943	4498

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/203,676	ZALUTSKY, MICHAEL R.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☐ Claim(s) *1-21 and 44-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-21 and 44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 1-21 and 44-47 are pending and under consideration.

3. Claims 1-9, 11-21 and 44-47 are under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

Claims 1-8, 11-21 and 44-47 are drawn to a composition for internally labeling a cell comprising a ligand which specifically binds to a surface antigen of a cell and is internalized by the cell, wherein the ligand is selected from the group consisting of an antibody, a fragment of an antibody, and a synthetic polypeptide. The nature of the composition is determined by the identify of the fragment of an antibody and a synthetic polypeptide in addition to the identity of the antibodies. thus, the claims encompass a genus of ligands which include antibodies, fragments of antibodies and synthetic polypeptide which bind to cell surface antigens and are subsequently internalized. The specification describes the binding of antibodies to the EGF variant III receptor and the subsequent internalization of said antibodies. the claims do not qualify the structure of the antibody fragments. When given the broadest reasonable interpretation, antibody fragment read on the immunoglobulin constant region which binds to the Fc receptor and is subsequently internalized. The genus of antibody fragments encompassed by the claims includes the Fc fragment of antibodies. The specification fails to describe any synthetic polypeptides which bind to cell surface antigens and are subsequently internalized. The genus of synthetic polypeptides is highly variant because it encompasses any peptide binding to any cell surface ligand. The disclosure of antibodies which bind to the EGF variant III receptor do not adequately describe a genus of ligands which include Fc fragments and synthetic polypeptides because said genus includes fragments and peptides which have widely differing structural ad functional attributes from the anti-EGF variant III antibodies. Claim 9 is drawn to the composition of claim 1 wherein the ligand binds to the EGF variant III receptor.

The scope of claim 9 includes synthetic polypeptides. The disclosure of the anti-EGF variant IIII receptor antibodies does not describe the claimed genus of synthetic polypeptides because the genus includes polypeptide that vary significantly in structure from the anti-EGF variant III receptor antibodies. One of skill in the art would conclude that applicant was not in possession of the claimed invention.

4. Claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199, cited in a previous Office action) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) in view of Barnett et al (CA 209465), Woo et al (U.S. 5,130,116), the abstract of Reist et al (Cancer research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140).

Claim 1 is drawn in part to a composition for internally labeling a cell comprising a ligand which specifically binds to a cell surface antigen and is internalized by the cell, wherein the ligand is an antibody, an oligopeptide which comprises at least one positively charged amino acid molecule and at least one D-amino acid residue, wherein the oligopeptide does not comprise two or more contiguous L-amino acids, wherein said oligopeptide is covalently bound to the ligand and wherein said oligopeptide does not specifically bind to the surface antigen, and a label which is covalently bound to the oligopeptide. Claim 3 embodies the composition of claim 1 wherein the label is defined by the chemical structure of II. Claim 4 embodies the composition of claim 3 wherein the label is selected from a group which consists of 5-iodo-3-pyridinecarboxylate, in part. Claim 5 embodies the composition of claim 1 wherein the ligand is a monoclonal antibody. Claim 8 embodies the composition of claim 1 wherein the ligand specifically binds to a tumor cell. Claim 9 embodies the composition of claim 1 wherein the ligand selectively binds to EGF variant III receptor. Claim 10 embodies the composition of claim 1 wherein the ligand is a monoclonal antibody that selectively binds to EGF variant III receptor. Claim 14 embodies the composition of claim 1 wherein the oligopeptide comprises D-Lys. Claims 15 and 16 embody the composition of claim 14 wherein the oligopeptide comprises D-Arg, and at least three D-Arg, respectively. Claims 17 and 18 embody the compositions of claims 1 and 8, respectively, wherein the label comprises a radionuclide. Claims 19 and 20

embody the composition of claim 17 wherein the radionuclide is an alpha, beta or gamma emitter, and wherein the radionuclide is selected from a group consisting in part of 125-I, respectively. Claim 44 embodies the composition of claim 1 wherein the oligopeptide comprises at least two positively charged amino acids.

Claim 28 is drawn to a compound for labeling a ligand which binds to a cell surface antigen comprising a molecule of structure I. Claim 35 embodies the composition of claim 28 wherein at least one amino acid is D-Lys. Claims 36 and 37 embody the composition of claim 35 wherein at least one amino acid residues is D-Arg and at least three amino acid residues are D-Arg, respectively. Claim 38 embodies the composition of claim 28 wherein the label has the structure of II. Claim 39 embodies the composition of claim 28 wherein the label is selected from a group consisting in part of 5-iododpyridine carboxylate. Claim 40 embodies the composition of claim 38 wherein the label comprises a radionuclide. Claims 41 and 42 embody the composition of claim 40, wherein the radionuclide is an alpha, beta or gamma emitter, and wherein the radionuclide is selected from a group consisting in part of 125-I, respectively.

The abstract of Reist et al (1996) teach that anti-EGF variant III receptor antibody (L8A4) labeled with SIPC yielded an increased level of tumor to tissue ratio versus antibodies labeled with the tryamine cellobiose method. SIPC is N-succinimidyl-5-iodo-3-pyridine carboxylate. Zalutsky et al teach how to make N-succinimidyl-5-iodo-3-pyridine carboxylate and how to use said compound in the labeling of an anti-CEA antibody (columns 13-14, examples 4-6). Neither Reist et al (1996) nor Zalutsky et al teach the oligopeptide of the instant invention.

Barnett et al teach compositions comprising chemical conjugates between a carrier peptide and an agent wherein the carrier peptide facilitates the delivery of said agent into the nucleus (page 1, lines 7-9). Barnett et al teach that said carrier peptide is comprised mainly of positively charged amino acids, at least 50% of which are in the D-form (page 2, lines 9-14). Barnett et al teach that both Arg and Lys are included in the scope of positively charged amino acids (page 3, lines 28-30). Barnett et al teach the specific embodiment of [D-Arg]9 as a specific embodiment (page 9, example 1), thus fulfilling the specific embodiments of claims drawn to oligopeptide which do not comprise two or more contiguous L-amino acids and claim 44 drawn to at least two positively charged amino acids. One of skill in the art would understand that D-

Lys could be substituted for any of the D-Arg in [D-Arg}9 and remain within the teachings of Barnett regarding positively charged D-amino acids, thus fulfilling the specific embodiment of claims 14-16. Barnett et al teach that the carrier peptide can be coupled to an agent which is also a peptide (page 6, lines 1-3). Barnett et al do not specifically teach the coupling of the carrier peptide to an antibody or ligand which binds to EGF variant III receptor, or the attachment of a radionuclide or the radiolabels of the instant invention.

Woo et al teach "Although not wishing to be bound by theory, it is necessary that in order for the present .sup.125 I labeled monoclonal antibody to be effective, the monoclonal antibody must first be internalized significantly into the cell as a result of binding to its specific membrane antigen. It is believed that for maximum cell killing efficiency of a 17-1A positive tumor, the .sup.125 I radio labeled monoclonal antibody or its radioactive breakdown products, must bind directly to the nucleus. The method of the present invention provides an effective method for localizing radiation to tumor cells. The method results in the radio labeled tumor specific antibody specifically targeting the tumor cell, and the evidence provided in the Examples below indicates that the antibody is internalized into the tumor cell, and the radionuclide is thereby placed in close proximity to the tumor cell nucleus. The radiation emitted by the Auger-electron emitter particularly lethal at this close range to the tumor cell, but not to surrounding tissue, due to its subcellular range. The radiation damage to the cells is ultimately due to chromosomal damage, which results in irreparable damage to, and provides efficient killing of the tumor cells". Thus Woo et al teach the delivery of 125-I via a monoclonal antibody which is internalized and that localization of 125-I to the cell nucleus is necessary for the optimum killing of tumor cells. Woo et al do not teach the oligopeptides of the instant invention, or the ligand which binds to the EGF variant III receptor.

The abstract of Reist et al (1995) teaches that anti-EGF variant III receptor antibodies are internalized at 37 degrees and are subsequently processed intracellularly by lysosomal degradation.

The abstract of Wikstrand et al teaches that the EGF variant III receptor is internalized, but is not found within the nucleus (lines 3-8 and 24-25 of the abstract). The abstract further teaches that said variant receptor is not expressed in normal tissues but is found in gliomas, non-

small cell lung and breast carcinomas and therefore provides a specific target for the selective delivery of toxins to these cancers.

It would have been prima facie obvious to incorporate the carrier peptide of Barnett into the SIPC labeled L8A4 antibody as taught by Reist et al (1996). One of skill in the art would be motivated to do so by the teachings of Woo et al on the desirability of localizing 125-I to the cell nucleus in order to maximize damage and subsequent cell killing to the targeted cell versus the surrounding cells, and the teachings the abstract of Wikstrand et al which indicate that the internalized variant EGF receptor is not located within the nucleus and the teaching of the abstract of Reist et al (1995) which indicate that antibodies which are bound to the variant receptor are degraded within the lysosomes. One of skill in the art would be motivated to re-direct the internalized labeled antibody from the lysosomes into the nucleus in order to maximize the accumulation of 125-I within the nucleus.

5. Claims 1, 3-6, 8-10, 14-20, 28, 30, 31, 35-42 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) and Barnett et al (CA 209465) and Woo et al (U.S. 5,130,116) and the abstract of Reist et al (Cancer Research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) for the reasons set forth in the rejection of claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42 and 44 above and in further view of Schlom (In: Molecular Foundations of Oncology, 1991, pp. 95-134).

The specific embodiments of claims , 3-5, 8-10, 14-20, 28, 35-42 and 44 and the teachings of Reist et al (1996) and Zalutsky et al and Barnett et al and Woo et al and the abstract of Reist et al (1995), and the abstract of Wikstrand et al which render the specific embodiments of said claims obvious is set forth above.

Claims 6 embodies the method of claim 1 wherein the ligand is an interspecies recombinant antibody. Claim 45 embodies the composition of claim 1 wherein the ligand is a fragment of an antibody comprising at least a portion of an immunoglobulin light chain variable region and at least a portion of an immunoglobulin heavy chain variable region. Claim 46 embodies the composition of claim 45 wherein the fragment comprises an immunoglobulin light

chain variable region and an immunoglobulin heavy chain variable region. Claim 47 embodies the composition of claim 1 wherein the ligand comprises a single chain Fv.

Neither of said prior art references teach a recombinant antibody, an antibody fragment or a scFv.

Schlom teaches that single chain Fv antibodies are better able to penetrate a tumor mass, avoid the induction of a HAMA response and clear the blood more rapidly that whole antibodies (pages 119-123 under the heading "Single Chain Antigen Binding Proteins").

It would have been prima facie obvious at the time the invention was made to substitute a recombinant single chain Fv antibody having the variable light chain and variable heavy chain of the anti-EGF variant III receptor for the L8A4 antibody as taught by Reist et al (1996). One of skill in the art would have been motivated to do so by the teachings of Schlom who address the advantages of single chain antibodies over full antibodies.

6. Claims 1, 3-6, 7-10, 14-20, 28, 30, 31, 35-42 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) and Zalutsky et al (U.S. 5,302,700, cited in a previous Office action) and Barnett et al (CA 209465) and Woo et al (U.S. 5,130,116) and the abstract of Reist et al (Cancer Research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) for the reasons set forth in the rejection of claims 1, 3-5, 8-10, 14-20, 28, 35-42 and 44 above and in further view of Schlom (In: Molecular Foundations of Oncology, 1991, pp. 95-134).

The specific embodiments of claims 1, 3-5, 8-10, 14-20, 28, 30, 31, 35-42 and 44 and the teachings of Reist et al (1996) and Zalutsky et al and Barnett et al and Woo et al and the abstract of Reist et al (1995), and the abstract of Wikstrand et al which render the specific embodiments of said claims obvious is set forth above.

Claim 7 embodies the composition of claim 1 wherein the ligand is a humanized antibody. Neither Reist et al (1996) nor Zalutsky et al nor Barnett et al nor Woo et al nor Reist et al nor Wikstrand et al teach a humanized antibody.

Schlom teaches that following one dose of murine monoclonal antibody, approximately 50% of patients develop HAMA and that this increases to 90% in patients receiving multiple

doses of murine monoclonal antibody. Schlom concludes that because of the HAMA response only the first dose of monoclonal antibody, or perhaps the first and second doses, actually reach the tumor site. Schlom states that it is unrealistic to assume that just one or two administrations of a monoclonal antibody based cancer therapeutic to be effective. Schlom teaches that the use of chimeric and humanized antibodies can circumvent the induction of HAMA (page 98, second column bridging paragraph to page 99, first column).

It would have been prima facie obvious at the time the invention was made to humanize the L8A4 antibody of Reist et al (1996). One of skill in the art would have been motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response in patients receiving antibody-based therapeutics.

7. Claims 1, 5, 8-10, 14-16, 21, 28, 30, 35-37, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Reist et al (Proc Annu Meet Am Assoc Cancer Res, 1996, Vol. 37, page A3199) in view of Barnett et al (CA 209465, full document), Woo et al (U.S. 5,130,116), the abstract of Reist et al (Cancer research, 1995, Vol. 55, pp. 4375-4382), and the abstract of Wikstrand et al (Cancer Research, 1997 September, Vol. 57, pp. 4130-4140) and Schmidt et al(US 4,614,723).

The abstract of Reist et al (1995) teaches that anti-EGF variant III receptor antibodies are internalized at 37 degrees and are subsequently processed intracellularly by lysosomal degradation.

The abstract of Wikstrand et al teaches that the EGF variant III receptor is internalized, but is not found within the nucleus (lines 3-8 and 24-25 of the abstract). The abstract further teaches that said variant receptor is not expressed in normal tissues but is found in gliomas, non-small cell lung and breast carcinomas and therefore provides a specific target for the selective delivery of toxins to these cancers.

Woo et al teach "Although not wishing to be bound by theory, it is necessary that in order for the present .sup.125 I labeled monoclonal antibody to be effective, the monoclonal antibody must first be internalized significantly into the cell as a result of binding to its specific membrane antigen. It is believed that for maximum cell killing efficiency of a 17-1A positive tumor, the .sup.125 I radio labeled monoclonal antibody or its radioactive breakdown products, must bind

directly to the nucleus. The method of the present invention provides an effective method for localizing radiation to tumor cells. The method results in the radio labeled tumor specific antibody specifically targeting the tumor cell, and the evidence provided in the Examples below indicates that the antibody is internalized into the tumor cell, and the radionuclide is thereby placed in close proximity to the tumor cell nucleus. The radiation emitted by the Auger-electron emitter particularly lethal at this close range to the tumor cell, but not to surrounding tissue, due to its subcellular range. The radiation damage to the cells is ultimately due to chromosomal damage, which results in irreparable damage to, and provides efficient killing of the tumor cells". Thus Woo et al teach the delivery of 125-I via a monoclonal antibody which is internalized and that localization of 125-I to the cell nucleus is necessary for the optimum killing of tumor cells. Woo et al do not teach the oligopeptides of the instant invention, or the ligand which binds to the EGF variant III receptor.

Barnett et al teach compositions comprising chemical conjugates between a carrier peptide and an agent wherein the carrier peptide facilitates the delivery of said agent into the nucleus (page 1, lines 7-9). Barnett et al teach that said carrier peptide is comprised mainly of positively charged amino acids, at least 50% of which are in the D-form (page 2, lines 9-14). Barnett et al teach that both Arg and Lys are included in the scope of positively charged amino acids (page 3, lines 28-30). Barnett et al teach the specific embodiment of [D-Arg]9 as a specific embodiment (page 9, example 1), thus fulfilling the specific embodiments of claims drawn to oligopeptide which do not comprise two or more contiguous L-amino acids and claim 44 drawn to at least two positively charged amino acids. One of skill in the art would understand that D-Lys could be substituted for any of the D-Arg in [D-Arg}9 and remain within the teachings of Barnett regarding positively charged D-amino acids, thus fulfilling the specific embodiment of claims 14-16. Barnett et al teach that the carrier peptide can be coupled to an agent which is also a peptide (page 6, lines 1-3). Barnett et al do not specifically teach the coupling of the carrier peptide to an antibody or ligand which binds to a cell surface receptor, or the attachment of fluorescent labels to the carrier peptide.

Schmidt et al teach fluorescent labels for conjugation to antibodies (claims 11 and 24).

It would have been prima facie obvious to attach the carrier peptide of Barnett and to substitute a fluorescent label as taught by Schmidt et al for the radioactive iodine label in the

composition comprising the L8A4 antibody as taught by Reist et al (1996). One of skill in the art would be motivated to do so in order to examine in vitro the amount of label accumulated in the nucleus relative to the cytoplasm. The substitution of a fluorescent label would be desirable for in vitro studies in order to eliminate the hazards associated with radioactive labeling. One of skill in the art would be motivated to re-direct the label to the cell nucleus by means of the carrier peptide taught by Barnett in light of the teachings of Woo et al regarding desirability of targeting the cell nucleus for radiolabel accumulation in order to maximize damage and subsequent cell killing to the targeted cell versus the surrounding cells, and the teachings the abstract of Wikstrand et al which indicate that the internalized variant EGF receptor is not located within the nucleus and the teaching of the abstract of Reist et al (1995) which indicate that antibodies which are bound to the variant receptor are degraded within the lysosomes.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 21, 2003